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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,865	12/08/2000	Edwin Oscar Schraa	2578-4257.1US	3138

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TRASK BRITT
P.O. BOX 2550
SALT LAKE CITY, UT 84110

EXAMINER

LI, QIAN J

ART UNIT	PAPER NUMBER
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1632

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DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/733,865

Applicant(s)

SCHRAA ET AL.

Examiner

Q. Janice Li

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 May 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 41-46 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 41-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 04 March 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed 5/28/03 has been entered and assigned as paper #15. Claims 1-3, 5, 7-10, 13, and 27-40 have been canceled, and claims 41-46 are newly submitted. Claims 41-46 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in paper #15 would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 7-9, 30, and 34-37 under 35 U.S.C. 112, first paragraph applies to new claims 41-46 for reasons of record and following.

Applicants argue in paper #15 that claims 41-46 do not recite, "delivering a gene of interest to a recipient cell", and that Harvey reference is inapplicable to a humoral response to adenovirus because the author acknowledges that the decreased humoral response may be due to a decrease in the effective administration of immunizing virus.

The arguments have been fully considered but they are not persuasive.

Although the preamble of claim 41 no longer recites, "delivering a gene of interest to a recipient cell", present claim recitation "administering a recombinant adenovirus containing a gene of interest to a human subject" requires delivering the gene of interest to a recipient cell in order for the gene of interest functional in the human subject. Therefore, the nature and the breadth of the claims have not changed.

The Harvey reference was relied on as a showing of the association between the type and degree of immune response and routes of administration, not as prior art, thus, it is applicable for the issue of whether the claims are enabled for gene delivery using an adenoviral vector through any route of administration.

The critical issue for whether the claimed invention is enabled concerns whether sequentially administering two adenoviral vectors reactive to the same type of antibody (preferably the same type of vector) could circumvent pre-existing immunity for repeated adenoviral vector administration in gene therapy. To this end, the specification only prophetically teaches the principle and the art of record teaches away from the instant claims. The Office cited *Parks et al* (Gene Ther 1999 Sept;6:1565-73), *Kass-Eisler* (Gene Ther 1996;3:154-620), *Mack* (Human Gene Ther 1997;8:99-109), and *Mastrangeli et al* (Human Gene Ther 1996;7:79-87) showing that the knowledge of the skilled has provided evidence contrary to the prophetic teaching of the specification. Thus, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed invention. However, applicants fail to respond to the issue, thus, in the absence of evidence to the contrary, the rejection stands.

Applicants' amendment triggered new grounds of rejection that appear below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 41-44, and 46 are newly rejected 35 U.S.C. 103(a) as being unpatentable over *Bramson et al* (Gene Ther 1997;4:1069-76, IDS).

Claims are drawn to a method for delivering a gene of interest to a human subject comprising first delivering an adenovirus lacking said gene of interest, allowing for neutralizing humoral response to said adenovirus to be raised, preferably more than 14 days, and administering an adenovirus comprising the gene of interest, wherein the gene of interest is interleukin. Optionally, a second dose of the adenovirus lacking said gene of interest is administered before administering the adenovirus comprising the gene of interest.

Bramson et al teach a gene delivery system comprising a wild-type adenovirus 5 (Ad5), and a recombinant Ad5 encoding IL-12 as gene of interest (AdmIL12). *Bramson et al* teach first intranasal administering 10^8 of Ad5 (adenovirus lacking the gene of interest), and 31 days later, administering 5×10^8 AdmIL12 (adenovirus encoding interleukin) intratumorally. *Bramson et al* go on to teach repeating the administration of

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adenovirus lacking IL-12 could further prevent viral dissemination to tissues other than tumor (left column, page 1072). *Bramson et al* administering the vectors in mice but not a human subject. However, they clearly teach that the mouse study is pre-clinical study for human gene therapy (Introduction and Discussion), indicating the intention and knowledge of using the vectors in gene therapy for humans.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the methods taught by *Bramson et al* in humans with a reasonable expectation of success once the pre-clinical trial has been proven safe and effective. The ordinary skilled artisan would have been motivated to do so as clearly taught by *Bramson et al*. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

In paper#15, applicants argue that *Bramson et al* use the method for a completely different reason unrelated to the teaching of the inventors, thus, a person of ordinary skill in the art would not be motivated by *Bramson et al* to actively induce the presence of neutralizing adenovirus antibodies in humans.

The argument has been fully considered but found not persuasive. This is because the method steps of *Bramson et al* meet the claim limitation, and there is no manipulative difference between the method steps of claimed invention and that of the prior art. Further, the intended use of the method does not constitute a step in the instant method as claimed. Even if the claim recites the intended use, such limitation bear little weight on the determination of novelty of the invention. This is because a recitation of the intended use of the claimed invention must result in a structural

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difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claims 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Bramson et al* (Gene Ther 1997;4:1069-76, IDS) as applied to claims 41-44 and 46, and in view of *Esandi et al* (Gene Ther 1998;5:778-88).

Bramson et al do not teach using a vector encoding an IL-3.

Esandi et al teach using an adenoviral vector encoding IL-3 in gene therapy for non-small cell lung cancer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector taught by *Bramson et al*, by simply substituting IL-12 with IL-3 as taught by *Esandi et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it is within the knowledge of the artisan to select a gene of interest for a particular need of therapy. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
July 30, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

